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Visible Light-Induced Ruthenium-Catalyzed Alkylation of Activated C(sp^3)–H bonds.

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In this issue of *Chem Catalysis*, Koenigs and co-workers report an efficient photocatalytic system for activated C(sp^3)–H bond functionalization at room temperature. The approach based on visible light-induced ruthenium catalysis allows for selective αC–H alkylation of amides under mild reaction conditions.

The direct and selective functionalization of C–H bonds is a particularly valuable synthetic tool which has found important applications in the construction of complex organic frameworks and in the late-stage modification of bioactive molecules.[1,2] The recent resurgence of visible light photoredox catalysis has enabled the development of new photocatalytic systems operating under mild reaction conditions and capable of promoting the functionalization of C–H bonds with high functional group tolerance and great selectivity, especially when a dual strategy combining photoredox and transition-metal catalysis is involved.[3] More recently, a particular attention has been given to visible light-induced transition-metal catalysis, where the transition metal complex is capable of both absorbing visible light and enabling catalysis in the absence of an exogeneous photosensitizer.[4] Unlike traditional transition metal-based photocatalysts such as Ru(II) polypyridyl and cyclometallated Ir(III) complexes that undergo outer sphere single-electron or energy transfer from their excited states, the alternative photoinduced catalysis occurs in the coordination sphere of the transition metal enabling bond braking/bond forming that would be unfeasible under non-irradiative conditions.[5] While this new approach represents a paradigm shift in catalysis,[6] examples implementing this strategy for the site selective functionalization of C(sp^3)–H bonds are still rather scarce.[7,8,9]

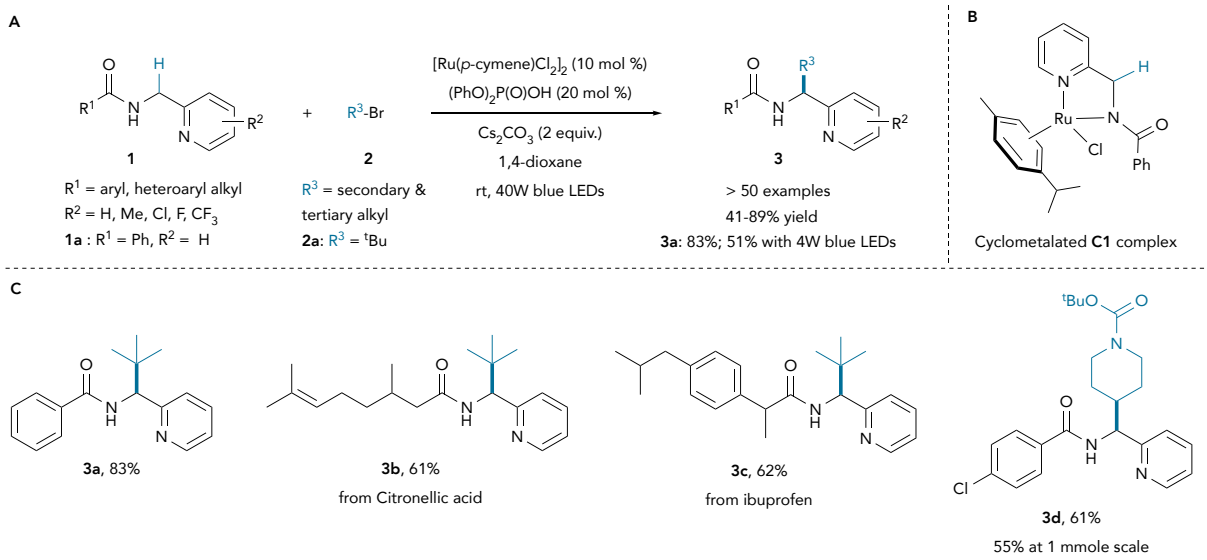
In this issue, Koenigs and co-workers use a ruthenium-based catalyst under visible light irradiation to perform room temperature alkylation of activated C(sp^3)–H bonds that are adjacent to an amide moiety.[10] The initial efforts were dedicated to the optimization of the reaction conditions using *N*-(pyridin-2-ylmethyl)benzamide **1a** as a model substrate, *tert*-butyl bromide **2a** as the alkylating agent, in the presence of Cs_2CO_3 as a base, Ru(p-cymene)$_2$ as catalyst, diphenyl hydrogen phosphate as co-catalyst, and irradiated with 4W blue LEDs (Scheme 1A). Under these conditions, the alkylation occurred selectively at the benzylic position adjacent to the amide moiety in 51% yield. The authors evidenced the importance of each of the reagents, and more importantly, demonstrated that the reaction did not proceed in the absence of light even when heating as high as 140°C. A noticeable improvement of the catalytic activity was observed when more powerful 40W blue LEDs (λ_{max} = 467 nm) were used, yielding 83% of the desired alkylated product **3a**. Under the optimized conditions, the on/off experiment indicated that constant irradiation was essential for the reaction to proceed.

The authors have made a great effort to gain a better understanding of the reaction mechanism by first performing various experiments in the presence of the cyclometalated

complex **C1** that is readily formed in the dark from $[Ru(cymene)Cl_2]_2$ and the amide substrate **1a** under basic condition at room temperature (Scheme 1B). While this complex displays broad absorbance in the visible region, no fluorescence could be detected precluding the possibility of conducting in-depth quenching experiments. Nevertheless, the authors could provide evidence that light plays a key role in the formation of the deprotonated cyclometalated ruthenium intermediate, which would subsequently undergo single electron transfer (SET) with the alkyl bromide substrate to form the corresponding alkyl radical. Computational studies tend to support this deprotonation-SET mechanism rather than a pathway involving first a SET from the photoexcited state of the cyclometalated ruthenium complex **C1**. The final step would involve alkyl radical addition to form the desired C–C bond and release of the expected product in the presence of a weak acid.

The developed methodology was ultimately applied to a large library of substrates demonstrating that variations both on the amide fragment and on the pyridine ring were well tolerated (Scheme 1A). Interestingly, amide substrates derived from natural products were efficiently engaged in the photocatalytic alkylation process that also perform well with secondary alkyl bromide partners giving direct access to drug precursors (Scheme 1C). The limitations lied in the use of primary alkyl bromide as alkylating agent and quinoline or pyrazine as directing groups.

By implementing visible light-induced transition metal catalysis for C–H bond functionalization, Koenigs and co-workers have achieved and elegant and selective α-alkylation of amides, providing access to various amidopyridine compounds of potential relevance to medicinal chemistry, natural product synthesis, or as ligands for metal complexes.



Scheme 1. A Visible Light-Induced Ruthenium Catalysis Enables Selective α-C–H bond functionalization of amides.
(A) Optimized reaction conditions for the C(sp^3)-H alkylation of amidopyridine substrates
(B) Visible light absorbing cyclometalated ruthenium complex.
(C) Selected examples of C-H alkylated products

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